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Impact of general anaesthesia in overall and disease-free survival compared to other types of anaesthesia in patients undergoing surgery for cutaneous melanoma: A systematic review and meta-analysis protocol.

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Keywords:	Melanoma, Analgesia, Anaesthesia, Cancer, Survival, Recurrence

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3	1	Title page
4 5	2	
5 7	3	Full title: Impact of general anaesthesia in overall and disease-free survival compared to other types of
3	4	anaesthesia in patients undergoing surgery for cutaneous melanoma: A systematic review and meta-
9	5	analysis protocol.
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52 53	35	Number of words without references and table: 2588
53 54	36	Figures: none
55	37	References:25
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40 Introduction: Cutaneous melanoma is an aggressive type of skin cancer. Anaesthetic agents may have an
41 impact on the immune response, postoperative neurohumoral response, and tumour progression.
42 Experimental data suggest that anaesthetics may influence the postoperative progression of melanoma.
43 This systematic review aims to evaluate the impact of general anaesthesia on overall and disease-free
44 survival compared to other types anaesthesia in patients undergoing surgery for cutaneous melanoma.

Methods and Analysis: The review will analyse data from controlled and observational studies of patients undergoing surgery for melanoma under general anaesthesia compared to other types of anaesthesia. The primary outcomes are 5-year overall survival and 2-year disease-free survival. The secondary outcomes include cost analysis and adverse events. A comprehensive literature search will be performed using the MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, LILACS, and IBECS databases. Grey literature will also be searched. Risk of methodological bias will be assessed using The Cochrane Collaboration's revised tool for assessing risk of bias in randomised trials (RoB 2.0) and the Newcastle-Ottawa scale for observational studies. Two reviewers will independently assess the eligibility of studies and risk of bias; a third author will solve discrepancies. One author will perform data extraction and the other will check the process and data. Qualitative analysis will be executed using all the included studies. A meta-analysis using a random-effects model for pooled risk estimates will be carried out for the two main outcomes if they conform to previously stated criteria. The GRADE approach will be used to summarise the quality of evidence. EndNote, Rayyan QCRI Cochrane Collaboration's Review Manager (RevMan) software and R software will be used for data management and statistical analysis.

59 Ethics and Dissemination: Ethics approval is not required as we analyse data from previously reported60 studies.

PROSPERO registration number: CRD42018114918.

62 Keywords: Melanoma, Anaesthesia, Analgesia, Cancer, Survival, Recurrence.

ARTICLE SUMMARY

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Strengths and limitations of this study

resource allocation.

included studies.

1 2

This review will be the first comprehensive systematic review designed specifically to assess the

The results of the systematic review will guide anaesthetists, surgeons, dermatologists, medical

The gaps of knowledge in this research field will be addressed, ensuring better research and

Conclusions and grading of recommendations may be limited by the number and design of

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impact of the anaesthetic technique on overall and disease-free survival in melanoma.

oncologists, and patients in clinical decision making.

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Cutaneous melanoma is the most lethal form of skin cancer.[1] It is the twenty-first most frequent cancer worldwide with a rising incidence, probably due to the increase in life expectancy.[2] Early stages of melanoma may be cured by excision of primary lesion, but advanced disease is still a challenge despite the recent advances in treatment. There are many factors that lead to a recurrence of cutaneous melanoma after primary surgery. The main prognostic factors are the histologic type, Breslow depth, cutaneous layer invasion (Clark level), regression, mitosis, ulceration on primary lesion, satellite and 'in transit' lesions, lymphatic involvement, and metastatic spread.[3]

Recently, the impact of the anaesthetic technique on recurrence rates of many types of tumours has been a
point of intense debate. Retrospective clinical evidence has found a protective effect of some anaesthetics
over others in many tumour types, including, but not limited to colon,[4] breast,[5] laryngeal,[6]
ovarian,[7] prostate,[8] bladder,[9] and cutaneous melanoma.[10]

Surgery can activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis.[11] This leads to an increase in the sympathetic tone, release of adrenocorticotropic hormone (ACTH), and synthesis of corticosteroids and catecholamines by the adrenal gland.[11] Thus, surgery is considered to be an important contributory factor for the clinical evolution of cancer. Inhalational anaesthetics are being investigated as an important facilitator for perioperative tumour dissemination.[12] They may cause inhibition of cellular immunity and promote angiogenesis and cellular proliferation.[13] Basic research in anaesthetic-induced organ protection provides important information regarding cellular signalling, especially, hypoxia-inducible factors (HIFs).[14] Halogenated inhalational anaesthetics can induce HIFs, possibly resulting in a cardiac, cerebral, hepatic, and renal cytoprotection described as 'anaesthetic preconditioning'.[14] The HIF system is essential for adaptation to the reduced supply of oxygen to healthy cells; however, it also helps the continued survival of tumour cells.[14] There is a large body of evidence regarding the relationship of HIFs with cancer.[15]

98 Experimental data support the hypothesis of anaesthetics influencing melanoma cells. Exposure to
99 halothane and isoflurane, when compared to oxygen, was correlated to an increased number of lung
100 metastasis in C57BL mice model injected with B16 melanoma cells.[16] In contrast, propofol induced

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apoptosis of B16F10 melanoma cells 'in vitro'.[17] Lidocaine and ropivacaine reduced the viability of
melanoma cells and increased apoptosis in a concentration-dependent manner 'in vitro'.[18]

103 Changes in institutional anaesthesia protocols to avoid general anaesthesia can impact the cost and the
104 overall safety of surgical procedure. Therefore, a systematic review and analysis of overall and disease105 free survival may modify clinical practice. This systematic review may influence the choice of anaesthetic

technique among anaesthetists, dermatologists, surgical oncologists, and patients.

107 The main objective of the proposed study is to evaluate the relationship between the anaesthetic technique108 and the overall and disease-free survival of malignant melanoma patients undergoing surgical resection.

109 The question formulated to fulfil the study objective is: Does general anaesthesia imply worse overall or

110 disease-free survival rate compared to other types of anaesthesia in patients undergoing surgery for

111 cutaneous melanoma? The secondary objectives are cost assessment and adverse events.

The systematic review protocol was designed according to the PRISMA-P statement.[19] The MOOSE proposal for reporting observational studies was also used as a reference for protocol development.[20] This systematic review has no specific funding. The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 16 November 2018 and was not updated (registration number CRD42018114918). In case of a protocol amendment, it will be described in detail, including the date and the rationale, and reported in the PROSPERO database. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

118 METHODS AND ANALYSIS

119 Eligibility criteria

120 Participants

121 The systematic review will include human studies evaluating patients undergoing surgery for cutaneous 122 melanoma. Non-cutaneous melanomas will not be included in the review. If the term 'melanoma' is 123 included in the text of the manuscript, it will be assumed to imply cutaneous melanoma, since it is the 124 most frequent subtype of the disease. Studies with less than 10 participants on each arm will be excluded. 125 No age, sex, or race restrictions will be applied. In case of studies that involve the overlap of patients, 126 only the most recent article will be chosen for inclusion.

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127 Study design

Randomised controlled trials (RCT) and observational studies (case control or cohort studies) will beincluded in the final analysis.

130 Interventions

131To be included in the review, the study must report a comparison of patients who undergo general

anaesthesia with other types of anaesthesia. Techniques other than general anaesthesia will be aggregatedas a single group in each study.

134 Outcomes

The aim is to assess if the use of general anaesthesia results in a higher risk of death or recurrence in melanoma patients. The main outcomes are 5-year overall survival and 2-year disease-free survival. Cost analysis and adverse events will be the secondary outcomes. Outcomes are not part of the eligibility criteria to be included in the review. Results of individual studies not including predefined outcomes will be reported in the body of the article or in an appendix according to the authors conclusions regarding the relevance of individual studies.

141 Timing

142 No timing restriction will be applied. All potentially relevant articles available in the selected databases
143 will be included in the review.

144 Setting and language

145 The initial triage of articles will require a title in English. No other language restrictions will be applied

and articles in other languages will be translated when necessary for analysing eligibility criteria,

147 evaluating risk of bias, and data extraction. The authors of the original articles will be contacted when

deemed necessary, first by email, and then through other digital platforms (e.g. LinkedIn, ORCID and
ResearchGate) and correspondence.

150 Information sources

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The main electronic databases accessed will be MEDLINE (PubMed interface), Excerpta Medica
database (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science
(online search engine, using all available databases), Latin American and Caribbean Health Sciences
Literature (in Portuguese: *Literatura Latino-Americana e do Caribe em Ciências da Saúde –* LILACS),
and The Spanish Bibliographic Index of the Health Sciences (in Spanish: *Índice Bibliográfico Español en Ciencias de la Salud -* IBECS). We will include studies published from the start of indexing until 30
October 2018.

158 Other sources

Hand searches of the first 200 citations on Google Scholar will be performed. Reference lists of the
included articles, reviews, and citing articles searched using the Web of Science database will be checked.
Grey literature will be searched using the Open Grey (http://www.opengrey.eu) and the Open Access
Theses and Dissertations (https://oatd.org) registries. The International Clinical Trials Registry Platform
search portal (http://apps.who.int/trialsearch) will also be accessed.

164 Search strategy

Search terms are designed to address the Patient, Intervention, Comparison, Outcome (PICO) standards. Patients will be searched using melanoma-related terms. For interventions and comparisons, anaesthesia related terms will be used. The authors of the systematic review decided to exclude the outcomes and any specific term related to the study design to increase the sensitivity of the search strategy. The specific search strategies were developed by one author (BLCA) and reviewed by a Health Science Librarian with expertise in systematic review searches. MEDLINE, EMBASE, and LILACS searches were chosen according to specific Medical Subject Headings (MeSH), Embase subject headings (Emtree) and Health Sciences Descriptors (in Portuguese: Descritores em Ciências da Saúde – DeCS) terms respectively. The search strategy for PubMed is described in Table 1 and the complete search strategies are reported in Appendix 1.

175 Table 1 PubMed search strategy

Database	Search

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PubMed	1 Anesthesia[MeSH Terms]
	2 Anesthetics[MeSH Terms]
	3 Anesthesiology[MeSH Terms]
	4 Anest*[Title/Abstract]
	5 Anaest*[Title/Abstract]
	6 Analg*[Title/Abstract]
	7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
	8 Melanoma[MeSH Terms]
	9 Melanoma*[Title/Abstract]
	10 #8 OR #9
	11 #7 AND #10
Data Managem	ent

177 EndNote web will be used for reference management; Rayyan (Qatar Computing Research Institute -

178 QCRI) web application will be used for the process of selection of studies. Cochrane Collaboration's

179 Review Manager (RevMan) software and R software will be used for systematic review data management180 and statistical analysis.

181 Selection of Studies

182 Two authors (BLCA and JOL) will check all the references in the databases. Independent evaluation will
183 be carried out using a stepwise approach for screening, eligibility, and inclusion of studies. Concordance
184 will be assessed by the kappa statistic in each step and reported. In the screening phase, articles selected
185 by at least one of the authors will be submitted to full-text evaluation in the eligibility phase if a
186 consensus is not reached between authors. Disagreements will be resolved by consensus or at the

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discretion of the senior researcher (LCST). One review author (BLCA) will extract the data to the
RevMan software and a second author (JLO) will check the process and the data collected.
Risk of Bias
The Cochrane Collaboration's revised tool for assessing the risk of bias in randomised trials (RoB 2.0)
will be used to evaluate RCT; the Newcastle-Ottawa scale will be used to assess methodological bias in
observational studies. The risk of bias assessment will be conducted by two authors (BLCA and JLO); in
case of disagreement, a third author (LCST) will arbitrate. The summary of the assessment of the risk of
bias in each category will be reported.
Publication Bias
If ten or more studies are included in the systematic review, a funnel plot visual analysis will be
performed for publication bias assessment.
Heterogeneity
Statistical heterogeneity will be assessed using Chi-squared (χ^2) and inconsistency (I ²) tests.
Heterogeneity will be quantified by the I ² test described in the Cochrane Handbook for Systematic
Reviews of Interventions and will be reported as low ($I^2=0-25\%$), moderate ($I^2=26-50\%$), or high
(I2>50%).[21] If, according to the judgement of the reviewers, clinical, methodological, and statistical
heterogeneities make pooling of data inappropriate for a specific outcome, the meta-analysis will be
omitted for this outcome. However, data of individual studies will be displayed as a forest plot for a better
appraisal of the results.
Qualitative analysis
Studies included in the review evaluating overall survival, disease-free survival, costs, and adverse events
as endpoints will be summarised in tables including authorship, year of publication, study sample, design,
interventions or arms, comparisons, reported outcomes, and results. Other details regarding study design
and quality of reports will also be described, addressing the strengths and weaknesses of the body of
evidence and how they impact the interpretation of the results of the meta-analysis.
Quantitative analysis

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Overall and disease-free survival analysis will be quantitatively evaluated if more than one study is included for a specific endpoint. For RCT and cohort studies data will be pooled based on relative risk estimation; adjusted data will be used to reduce confounding risk in observational studies if possible. Effect size will be measured with 95% confidence intervals (CI), and significance will be set at P < 0.05, with the study as the unit of analysis. Case-control studies will be reported using odds ratio as the summary measure, and the data from this type of studies will be reported separately. If it is not possible to extract relative risk data from other sources, Kaplan-Meyer curves will be the source of the data, using a pixel-coordinate method of mapping the axes of interest and calculation of percentages. A broad definition regarding patient selection in studies will be used, permitting the inclusion of different stages, surgical procedures, and control groups between studies. A random effects model will be chosen to perform the meta-analysis considering anticipated clinical and methodological heterogeneity. If 5-year overall survival is reported, it will be the preferred follow-up period for relative risk analysis. If 5-year survival is not reported, we will attempt to contact the authors for this information; if no contact is possible, the longest reported follow-up period will be chosen. Two-year disease-free survival will be chosen as the other study outcome. These preferred periods of follow-up were chosen according to recent recommendations regarding postoperative cancer outcomes.[22] Results will be aggregated independent to the duration of follow-up. The inclusion of trials outside the target follow-up period will increase the power of the review without impacting the goals of the review. A sensitivity analysis will be performed excluding studies with follow-up periods other than 5-year overall and 2-year disease-free survival. Sensitivity analysis will also be carried out after excluding studies that are observational in design and assessed to have a high risk of bias to evaluate the impact of clinical and methodological heterogeneity on outcomes. The year of publication (to assess changes in therapy over time) and the anaesthetic technique used in the control group (local, regional, and both) will be used as parameters to perform a metaregression and subgroup analysis.

237 Quality of the Body of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to
summarise the quality of evidence for each outcome will be applied.[23] The GRADE rating scale assigns
high, moderate, low, or very low reliability categories to a body of evidence as detailed elsewhere. [23]

241 Discussion

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Some of the previous systematic reviews investigating the relationship between exposure to anaesthetic
agents on survival and oncologic outcomes included different cancer types and anaesthetic agents in the
same evaluation.[24, 25] Cancer cannot be treated as a single disease or a group of diseases with a similar
response to various treatment modalities. Therefore, systematic reviews on this topic should consider
relevance to specific types of cancer regarding tumour biology and specific surgical techniques employed,
despite the lack of prospective studies in this field.

248 The inclusion of cohort and case-control studies in the systematic review may be an expected source of 249 bias. The association between anaesthetic technique and oncologic outcomes is not an anticipated 250 endpoint of therapy; we aim to assess the possibility of unexpected harm in this systematic review. 251 Unequivocal evidence of association of the anaesthetic technique with survival outcomes through 252 randomised controlled trials may take several decades to establish. Such studies are expensive, take a long 253 period of time, and require extensive follow-up. Hence, they are usually outside the scope of regular 254 anaesthesia research. Decision-making is complex in the absence of such high-quality evidence, because 255 evidence of harm is difficult to establish, though harm may occur in some instances. Therefore, 256 observational data must be carefully assessed, especially when prospective data is inadequate. Adjusted 257 data from observational studies by pooled-analysis will be used to overcome confounding factors. 258 Subgroup analyses will address the influence of different study designs on the effect measure of this 259 meta-analysis.

A recent consensus of experts in the field of anaesthesiology defined the main outcomes to be chosen when evaluating the impact of anaesthesia techniques on cancer outcomes.[22] The endpoints chosen for this systematic review are based on this report. A uniform definition of outcomes of interest is essential to carry out future observational studies and clinical trial protocols.

264 ETHICS AND DISSEMINATION

265 This study is a systematic review with meta-analysis that evaluates data from previously reported studies;266 hence ethical approval is not required. We plan to publish this study in a peer-reviewed journal.

Author Contributions: BLCA is the guarantor of the review and drafted the manuscript. All authors
 contributed to the inclusion criteria, the risk of bias assessment, and data extraction strategies. FMC and
 LESF contributed with their knowledge on systematic reviews. LCST and FMC will contribute with

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3 4	270	epidemiological and statistical analysis. ACM contributed through expertise in medical, and JLO, through
5	271	expertise in surgical oncology. BLCA contributed with anaesthetic knowledge. BLCA and JLO will
6 7	272	screen potential studies, perform duplicate independent data extraction, risk of bias assessment, GRADE
8 9	273	assessment. LCST will act as a third reviewer and arbitrator if necessary. All authors read, provided
10 11	274	comments, and approved the final version of the protocol.
12		
13 14	275	Acknowledgements: We are grateful to acknowledge to Raphael Chanca, the Health Science Librarian
15 16	276	who reviewed the systematic review search strategy.
17 18		
19	277	Funding: The authors have not received a specific grant for this research from any funding agency in the
20 21	278	public, commercial, or not-for-profit sectors.
22 23		
24	279	Competing interests: None declared.
25		
26 27	280	Patient consent: Not required.
28		
29	281	Provenance and peer review: Not commissioned; externally peer reviewed.
30 31		
32	282	Data sharing statement: No additional data from this study are available.
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Appendix 1

Complete search Strategy

Database	Search
Pubmed	1 Anesthesia[MeSH Terms]
	2 Anesthetics[MeSH Terms]
	3 Anesthesiology[MeSH Terms]
	4 Anest*[Title/Abstract]
	5 Anaest*[Title/Abstract]
	6 Analg*[Title/Abstract]
	7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
	8 Melanoma[MeSH Terms]
	9 Melanoma*[Title/Abstract]
	10 #8 OR #9
	11 #7 AND #10
Embase	1 'melanoma'/exp
	2 'fortner melanoma':ti,ab
	3 'malignant melanoma':ti,ab
	4 'malignant melanomatosis':ti,ab
	5 'melanocarcinoma':ti,ab
	6 'melanoma':ti,ab
	7 'melanoma (e)':ti,ab
	7 'melanoma (e)':ti,ab8 'melanomalignoma':ti,ab
	9 'naevi and melanomas':ti,ab
	10 'naevocarcinoma':ti,ab
	11 'nevi and melanomas':ti,ab
	12 'nevocarcinoma':ti,ab
	13 'nodular melanoma':ti,ab
	14 'pigmentary cancer':ti,ab
	15 #1 OR# 2 OR #3 OR #4# OR # 5# OR #6# OR# 7
	OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
	OR #14

1 2		
3 4		16 'anesthesiological procedure'/exp
5		17 'anaesthesia and analgesia':ti,ab
6 7		18 'anesthesia and analgesia':ti,ab
8 9		19 'anesthesiological procedure':ti,ab
10		20 'anesthesiological techniques':ti,ab
11 12		21 'anesthetic agent'/exp
13 14		22 'anaesthetic':ti,ab
15 16		23 'anaesthetic agent':ti,ab
17		24 'anaesthetic drug':ti,ab
18 19		25 'anaesthetics':ti,ab
20 21		26 'anaesthetics, combined':ti,ab
22 23		27 'anaesthetics, dissociative':ti,ab
24		28 'anaesthetics, general':ti,ab
25 26		29 'anesthetic':ti,ab
27 28		30 'anesthetic agent':ti,ab
29		31 'anesthetic drug':ti,ab
30 31		32 'anesthetics':ti,ab
32 33		33 'anesthetics, combined':ti,ab
34 35		34 'anesthetics, dissociative':ti,ab
36		35 'anesthetics, general':ti,ab
37 38		36 'general anaesthetic':ti,ab
39 40		37 'general anaesthetic agent':ti,ab
41 42		38 'general anesthetic':ti,ab
43		39 'general anesthetic agent':ti,ab
44 45		40 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR
46 47		#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR
48		#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR
49 50		#34 OR #35 OR #36 OR #37 OR #38 OR #39)
51 52		41 #15 AND #40
53 54	CENTRAL	1 MeSH descriptor: [Anesthesia] explode all trees
55		2 MeSH descriptor: [Anesthetics] explode all trees
56 57		3 MeSH descriptor: [Anesthesiology] explode all
58 59		trees
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4 Anest*:ab,ti,kw
5 Anaest*:ab,ti,kw
6 #1 OR #2 OR #3 OR #4 OR #5
7 MeSH descriptor: [Melanoma] explode all trees
8 Melanoma*:ab,ti,kw
9 #7 OR #8
10 #6 AND #9
1 TS=(Anest* OR Anaest*)
2 TS=(Melanoma*)
3 #1 AND #2
1 mh:("anesthesia")
2 mh:("anesthesia and analgesia")
3 mh:("analgesia and anesthesia")
4 mh:("analgesia")
5 tw:(anest*)
6 tw:(analg*)
7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
8 mh:(Melanoma)
9 tw:(Melanoma*)
10 #8 OR #9
11 #7 AND #10
In the Advanced Search
Title: Anest* OR Anaest* OR Analg*
Condition: Melanoma
Recruitment status: All
1 Anest*
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Open Access	1 Anest*
Theses and	2 Anaest*
Dissertations	3 Analg*
	4 #1 OR #2 OR #3
	5 Melanoma*
	6 #4 AND #5
Google	anesthesia AND melanoma
Scholar	

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 PRISMA-P 2015 Checklist
 Preferred reporting

 This checklist has been adapted for use with protocol submissions to Systematic Reviews from Table 3 in Moher D et al: Preferred reporting
 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reverse 2015 4:1

Section/topic	#		Informatior Yes	n reported No	Line number(s)
ADMINISTRATIVE IN	FORMAT		100		
Title					
Identification	1a	Identify the report as a protocol of a systematic review	\square		3-5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	\square		115,116
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number Abstract	$\overline{\boxtimes}$		61
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	\square		7-32
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	\square		267-274
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, gdentify as such and list changes; otherwise, state plan for documenting important protocol amendments	\square		116-117
Support					
Sources	5а	Indicate sources of financial or other support for the review	\square		114
Sponsor	5b	Provide name for the review funder and/or sponsor	\square		114
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	\square		114
INTRODUCTION		ies at			
Rationale	6	Describe the rationale for the review in the context of what is already known	\square		74-102
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	\boxtimes		107-111



Page 21	of	21	
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Section/topic	#	BMJ Open by copyright, include Checklist item	Information	n reported	Line
Section/topic	#		Yes	No	number(s)
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and reported g characteristics (e.g., years considered, language, publication status) to be used as criteriation status to be used as criteriation status and the status of the review			119-149
nformation sources	9	eligibility for the review Describe all intended information sources (e.g., electronic databases, contact with study 銀崎客s, trial registers, or other grey literature sources) with planned dates of coverage	\square		150-163
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including			164-175
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the to be a set of the set o			176-180
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) and search phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	\square		181-188
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done indep and in duplicate), any processes for obtaining and confirming data from investigators			181-188
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	\square		206-230
Dutcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and gadditional outcomes, with rationale	\square		134-140
Risk of bias in ndividual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	\square		189-194
DATA	•				
	15a	Describe criteria under which study data will be quantitatively synthesized			206-211
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, net the ds of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., <i>I</i> ² , Kendall's tau)			198-202; 212-230
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-			230-236
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned			202-205
leta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)			195-197
confidence in umulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)			223-240



Impact of general anaesthesia in overall and disease-free survival compared to other types of anaesthesia in patients undergoing surgery for cutaneous melanoma: A systematic review and meta-analysis protocol.

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-027993.R1
Article Type:	Protocol
Date Submitted by the Author:	22-May-2019
Complete List of Authors:	Araujo, Bruno; National Cancer Institute of Brazil , Anaesthesiology - Hospital do Câncer II de Oliveira, Jadivan; National Cancer Institute of Brazil , Conective and Bone Tissue Section, Hospital do Câncer II Corrêa, Flavia; National Cancer Institute of Brazil , Health Technology Assessment Unit, Population Research Division Fontes, Luis; Petrópolis Medical School, Department of Evidence-Based Medicine, Intensive Care, Gastroenterology de Melo, Andreia; National Cancer Institute of Brazil , Clinical Research Division, National Cancer Institute of Brazil (INCA) Thuler, Luiz; Brazilian National Cancer Institute , Clinical Research Division; Federal University of Rio de Janeiro State, Postgraduate Program in Neurosciences
Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Surgery, Dermatology, Oncology
Keywords:	Melanoma, Analgesia, Anaesthesia, Cancer, Survival, Recurrence

SCHOLARONE[™] Manuscripts

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7 8	4	anaesthesia in patients undergoing surgery for cutaneous melanoma: A systematic review and meta-
9	5	analysis protocol.
10 11	6	
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47	31	Fax: 00-55-21-32072964.
48 49	32	Email: brunoaraujomed@yahoo.com.br
50	33	
51 52	34	Number of words with references and table: 4004
52 53	35	Number of words without references and table: 2993
54	36	Figures: none
55 56	37	References: 28
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39 ABSTRACT

 Introduction: Cutaneous melanoma is an aggressive type of skin cancer. Anaesthetic agents may have an
 impact on the immune response, postoperative neurohumoral response, and tumour progression. This
 systematic review aims to evaluate the impact of general anaesthesia on overall and disease-free survival
 compared to other types anaesthesia in patients undergoing surgery for cutaneous melanoma.

Methods and analysis: The review will analyse data from controlled and observational studies of patients undergoing surgery for melanoma under general anaesthesia compared to other types of anaesthesia. The primary outcomes are overall survival and disease-free survival. The secondary outcomes are health-related quality of life, time to tumour progression, distant disease-free survival, time to treatment failure, cancer-specific survival, biochemical recurrence, return of intended oncologic therapy, days alive and out of the hospital at 90 days, cost analysis, and adverse events. A comprehensive literature search will be performed using the MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, LILACS, and IBECS databases. Grey literature will also be searched. Risk of methodological bias will be assessed using The Cochrane Collaboration's revised tool for assessing risk of bias in randomised trials (RoB 2.0) and the Newcastle-Ottawa scale. Two reviewers will independently assess the eligibility of studies and risk of bias; a third author will solve discrepancies. One author will perform data extraction and the other will check the process and data. Qualitative analysis will be carried out using all included studies. A meta-analysis using a random-effects model for pooled risk estimates will be carried out for the two main outcomes and for selected secondary outcomes if they conform to previously stated criteria. The GRADE approach will be used to summarise the quality of evidence.

59 Ethics and dissemination: Ethics approval is not required as we analyse data from previously reported60 studies.

- **PROSPERO registration number:** CRD42018114918.
- 62 Keywords: Melanoma, Anaesthesia, Analgesia, Cancer, Survival, Recurrence.

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ARTICLE SUMMARY

analysis.

bias.

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Strengths and limitations of this study

1 2

This will be the first comprehensive systematic review designed specifically to assess the impact

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The inclusion of non-randomised studies is both a strength and a limitation of the protocol.

randomised trials, limiting the influence of study design on the effects measured in this meta-

A rigorous and sensitive search will be performed to maximise comprehensiveness and minimise

The Grading of Recommendations, Assessment, Development and Evaluation approach will be

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Observational studies will not be combined with randomised controlled trials and quasi-

of anaesthetic technique on overall and disease-free survival in melanoma.

used to inform conclusions in an appropriate manner.

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Cutaneous melanoma is the most lethal form of skin cancer.[1] It is the twenty-first most frequent cancer worldwide with a rising incidence, probably due to the increase in life expectancy.[2] Early stages of melanoma may be cured by excision of primary lesion, but advanced disease is still a challenge despite the recent advances in treatment. There are many factors that lead to a recurrence of cutaneous melanoma after primary surgery. The main prognostic factors are the histologic type, Breslow depth, cutaneous layer invasion (Clark level), regression, mitosis, ulceration on primary lesion, satellite and 'in transit' lesions, lymphatic involvement, and metastatic spread.[3]

Recently, the impact of the anaesthetic technique on recurrence rates of many types of tumours has been a
point of intense debate. Retrospective clinical evidence has found a protective effect of some anaesthetics
over others in many tumour types, including, but not limited to colon,[4] breast,[5] laryngeal,[6]
ovarian,[7] prostate,[8] bladder,[9] and cutaneous melanoma.[10]

Surgery can activate the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis.[11] This leads to an increase in the sympathetic tone, release of adrenocorticotropic hormone, and synthesis of corticosteroids and catecholamines by the adrenal gland [11] Thus, surgery is considered to be an important contributory factor for the clinical evolution of cancer. Inhalational anaesthetics are being investigated as an important facilitator for perioperative tumour dissemination.[12] They may cause inhibition of cellular immunity and promote angiogenesis and cellular proliferation.[13] Basic research in anaesthetic-induced organ protection provides important information regarding cellular signalling, especially, hypoxia-inducible factors (HIFs).[14] Halogenated inhalational anaesthetics can induce HIFs, possibly resulting in a cardiac, cerebral, hepatic, and renal cytoprotection described as 'anaesthetic preconditioning'.[14] The HIF system is essential for adaptation to the reduced supply of oxygen to healthy cells; however, it also helps the continued survival of tumour cells.[14] There is a large body of evidence regarding the relationship of HIFs with cancer.[15]

Experimental data support the hypothesis of anaesthetics influencing melanoma cells. Exposure to
halothane and isoflurane, when compared to oxygen, was correlated to an increased number of lung
metastasis in C57BL mice model injected with B16 melanoma cells.[16] In contrast, propofol induced
apoptosis of B16F10 melanoma cells 'in vitro'.[17] Lidocaine and ropivacaine reduced the viability of

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Participants

108	melanoma cells and increased apoptosis in a concentration-dependent manner 'in vitro'.[18] The first
109	report of impaired survival associated with the use of general anaesthesia for melanoma surgery was
110	published by Seebacher et al; subsequent investigators achieved conflicting results.[10,19-21]
111	Changes in institutional anaesthesia protocols to avoid general anaesthesia can impact the cost and the
112	overall safety of surgical procedure. Therefore, a systematic review and analysis of overall and disease-
113	free survival may modify clinical practice. This systematic review may influence the choice of anaesthetic
114	technique among anaesthetists, dermatologists, surgical oncologists, and patients.
115	The main objective of the proposed study is to evaluate the relationship between the anaesthetic technique
116	and the overall and disease-free survival of malignant melanoma patients undergoing surgical resection.
117	The question formulated to fulfil the study objective is: Does general anaesthesia imply worse overall or
118	disease-free survival rate compared to other types of anaesthesia in patients undergoing surgery for
119	cutaneous melanoma? The secondary objectives are assessment of health-related quality of life, time to
120	tumour progression, distant disease-free survival, time to treatment failure, cancer-specific survival,
121	biochemical recurrence, return of intended oncologic therapy, days alive and out of the hospital at 90
122	days, costs, and adverse events.
123	This systematic review protocol was designed in accordance with the PRISMA-P statement.[22] The
124	MOOSE proposal for reporting observational studies was also used as a reference for protocol
125	development.[23] This systematic review has no specific funding. The systematic review protocol was
126	registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 16
127	November 2018 and has not been updated (registration number CRD42018114918). A protocol
128	amendment with the modifications of the systematic review protocol following the peer reviewduring the
129	BMJ Open editorial process will be described in detail, including the date and the rationale; this will be
130	reported in the PROSPERO database.
131	METHODS AND ANALYSIS
132	Eligibility criteria
133	Participants

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 The systematic review will include human studies evaluating patients undergoing surgery for cutaneous melanoma. Non-cutaneous melanomas will not be included in the review. If the term 'melanoma' is included in the text of the manuscript, it will be assumed to imply cutaneous melanoma, since it is the most frequent subtype of the disease. Studies with fewer than 10 participants on each arm will be excluded. No age, sex, or race restrictions will be applied. In case of studies that involve the overlap of patients, only the most recent article will be chosen for inclusion. Study design Randomised controlled trials (RCTs), quasi-randomised trials, and non-randomised studies (cohort and case-control studies) will be included in the final analysis. Interventions To be included in the review, the study must report a comparison of patients who underwent general anaesthesia with other types of anaesthesia. Techniques other than general anaesthesia will be aggregated as a single group in each study. Outcomes The aim is to assess if the use of general anaesthesia results in a higher risk of death or recurrence in melanoma patients. The primary outcomes are overall survival and disease-free survival. The secondary ouctomes are health-related quality of life, time to tumour progression, distant disease-free survival, time to treatment failure, cancer-specific survival, biochemical recurrence, return of intended oncologic therapy, days alive and out of the hospital at 90 days, cost analysis, and adverse events. Outcomes are not part of the eligibility criteria to be included in the review. Results of individual studies not including predefined outcomes will be reported in the body of the article or in an appendix according to the authors conclusions regarding the relevance of individual studies. Timing No timing restriction will be applied. All potentially relevant articles available in the selected databases will be included in the review. Setting and language

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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- 3 4	160	The initial triage of articles will require a title in English. No other language restrictions will be applied
5 6	161	and articles in other languages will be translated when necessary for analysing eligibility criteria,
7 8	162	evaluating risk of bias, and data extraction. The authors of the original articles will be contacted when
9	163	deemed necessary, first by email, and then through other digital platforms (e.g. LinkedIn, ORCID and
10 11	164	ResearchGate) and correspondence.
12 13 14 15	165	Information sources
16 17	166	The main electronic databases accessed will be MEDLINE (PubMed interface), Excerpta Medica
18 19	167	database (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science
20 21	168	(online search engine, using all available databases), Latin American and Caribbean Health Sciences
22 23	169	Literature (in Portuguese: Literatura Latino-Americana e do Caribe em Ciências da Saúde – LILACS),
24 25	170	and The Spanish Bibliographic Index of the Health Sciences (in Spanish: Índice Bibliográfico Español en
26 27	171	Ciencias de la Salud - IBECS). We will include studies published from the start of indexing until 30
28	172	October 2018.
29 30 31 32	173	Other sources
33 34	174	Hand searches of the first 200 citations on Google Scholar will be performed. Reference lists of the
35 36	175	included articles, reviews, and citing articles searched using the Web of Science database will be checked.
37 38	176	Grey literature will be searched using the Open Grey (http://www.opengrey.eu) and the Open Access
39 40	177	Theses and Dissertations (https://oatd.org) registries. The International Clinical Trials Registry Platform
41 42	178	search portal (http://apps.who.int/trialsearch) will also be accessed.
43 44 45 46	179	search portal (http://apps.who.int/trialsearch) will also be accessed. Search strategy
47 48	180	Search terms are designed to address the Patient, Intervention, Comparison, Outcome (PICO) standards.
49 50	181	Patients will be searched using melanoma-related terms. For interventions and comparisons, anaesthesia
51 52	182	related terms will be used. The authors of the systematic review decided to exclude the outcomes and any
52 53 54	183	specific term related to the study design to increase the sensitivity of the search strategy. The specific
55	184	search strategies were developed by one author (BLCA) and reviewed by a Health Science Librarian with
56 57	185	expertise in systematic review searches. MEDLINE, EMBASE, and LILACS searches were chosen
58 59 60	186	according to specific Medical Subject Headings (MeSH), Embase subject headings (Emtree) and Health

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> 187 Sciences Descriptors (in Portuguese: Descritores em Ciências da Saúde - DeCS) terms, respectively. The

188 search strategy for PubMed is described in Table 1 and the complete search strategies are reported in

189 Appendix 1.

190 Table 1 PubMed search strategy

Database	Search
PubMed	1 Anesthesia[MeSH Terms]
	2 Anesthetics[MeSH Terms]
	3 Anesthesiology[MeSH Terms]
	4 Anest*[Title/Abstract]
	5 Anaest*[Title/Abstract]
	6 Analg*[Title/Abstract]
	7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
	8 Melanoma[MeSH Terms]
	9 Melanoma*[Title/Abstract]
	10 #8 OR #9
	11 #7 AND #10

191

192 EndNote web will be used for reference management; Rayyan (Qatar Computing Research Institute -193 QCRI) web application will be used for the process of selection of studies. Cochrane Collaboration's 194 Review Manager (RevMan) software and R software will be used for systematic review data management 195 and statistical analysis.

196 **Selection of Studies**

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Two authors (BLCA and JOL) will check all the references in the databases. Independent evaluation will be carried out using a stepwise approach for screening, eligibility, and inclusion of studies. Interrater agreement within the screening process will be assessed by using Cohen's kappa statistic in each step and reported.[24] In the screening phase, articles selected by at least one of the authors will be submitted to full-text evaluation in the eligibility phase if a consensus is not reached between authors. Disagreements will be resolved by consensus or at the discretion of the senior researcher (LCST). One review author (BLCA) will extract the data to the RevMan software and a second author (JLO) will check the process and the data collected.

205 Risk of Bias

The Cochrane Collaboration's revised tool for assessing the risk of bias in randomised trials (RoB 2.0)
will be used to evaluate RCTs; the Newcastle-Ottawa scale will be used to assess methodological bias in
observational studies. The risk of bias assessment will be conducted by two authors (BLCA and JLO); in
case of disagreement, a third author (LCST) will arbitrate. The summary of the assessment of the risk of
bias in each category will be reported.

211 Publication Bias

212 If ten or more studies are included in the systematic review, a funnel plot visual analysis will be

213 performed for publication bias assessment.

214 Heterogeneity

215 Statistical heterogeneity will be assessed using Chi-squared (χ^2) and inconsistency (I²) tests.

216 Heterogeneity will be quantified by the I² test described in the Cochrane Handbook for Systematic

217 Reviews of Interventions and will be reported as low ($I^2=0-25\%$), moderate ($I^2=26-50\%$), or high

218 (I2>50).[24] If, according to the judgement of the reviewers, clinical, methodological, and statistical

219 heterogeneities make pooling of data inappropriate for a specific outcome, the meta-analysis will be

220 omitted for this outcome. However, data of individual studies will be displayed as a forest plot for a better

appraisal of the results.

222 Qualitative analysis

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223 The studies included in the review evaluating the primary and secondary outcomes will be summarised in224 tables including authorship, year of publication, study sample, design, interventions or arms,

225 comparisons, reported outcomes, and results. Other details regarding study design and quality of reports

will also be described, addressing the strengths and weaknesses of the body of evidence and how they

227 impact the interpretation of the results of the meta-analysis.

228 Quantitative analysis

RCTs and quasi-randomised trials will be pooled separately from observational studies for meta-analysis to reduce methodological heterogeneity. Overall and disease-free survival analysis will be quantitatively evaluated if more than one study with the same design is included for a specific endpoint. A meta-analysis will also be performed if more than one study reports the secondary outcomes time to tumour progression, distant disease-free survival, time to treatment failure, cancer specific survival, return of intended oncologic therapy, and days alive and out of hospital at 90 days. Hazards ratio (HR) estimation will be used as the summary measure for RCTs, quasi-randomised trials, and cohort studies; however, days alive out and of the hospital at 90 days will be evaluated using odds ratios, independent of study design. Case-control studies will be reported using odds ratios as the summary measure, and the data from this type of study will be reported separately. Effect size will be measured with 95% confidence intervals, and significance will be set at P<0.05, with the study as the unit of analysis. Adjusted data will be used if available, to reduce the risk of confounding in observational studies. The use of an adjusted estimate has a higher priority than requiring a similar period of follow-up across studies, because reduction of confounding factors is critical in ensuring the generality of the results. If it is not possible to extract HR data from other sources, Kaplan–Meier curves will be the source of the data, using a pixel-coordinate method of mapping the axes of interest and calculation of percentages. If 5-year overall survival is reported, it will be the preferred follow-up period for HR analysis. When 5-year survival is not reported, we will attempt to contact the authors for this information; if no contact is possible, the longest reported follow-up period will be chosen. Two-year disease-free survival will be used as the other study outcome. These preferred periods of follow-up were chosen in accordance with recent recommendations for analyses of postoperative cancer outcomes. [25] For the secondary outcomes of time-to-event data, the longest reported follow-up period will be used. Minimum follow-up required to be included in the meta-analysis for the time-to event data is estimated at 2 years. Results will be aggregated independent of the

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duration of follow-up if longer than 2 years. The inclusion of trials outside the target follow-up period will increase the power of the review without impacting the goals of the review. A broad definition regarding patient selection in studies will be used, permitting the inclusion of different stages, surgical procedures, and control groups between studies. A random effects model will be used to perform the meta-analysis, considering the anticipated clinical and methodological heterogeneity. A sensitivity analysis will be performed excluding studies with follow-up periods other than 5-year overall and 2-year disease-free survival. Sensitivity analysis will also be carried out after excluding studies that are judged to have a risk of bias to evaluate the impact of clinical and methodological heterogeneity on outcomes. The vear of publication (to assess changes in therapy over time) and the anaesthetic technique used in the control group (local, regional, and both) will be used as parameters to perform a meta-regression and subgroup analysis.

263 Quality of the Body of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to
summarise the quality of evidence for each outcome will be applied.[26] The GRADE rating scale assigns
high, moderate, low, or very low reliability categories to a body of evidence as detailed elsewhere.[26]

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267 DISCUSSION

Some of the previous systematic reviews investigating the relationship between exposure to anaesthetic agents on survival and oncologic outcomes included different cancer types and anaesthetic agents in the same evaluation.[27, 28] Cancer cannot be treated as a single disease or a group of diseases with a similar response to various treatment modalities. Therefore, systematic reviews on this topic should consider relevance to specific types of cancer regarding tumour biology and specific surgical techniques employed, despite the lack of prospective studies in this field.

The inclusion of cohort and case-control studies in the systematic review may be an expected source of
bias. The association between anaesthetic technique and oncologic outcomes is not an anticipated
endpoint of therapy; we aim to assess the possibility of unexpected harm in this systematic review.
Unequivocal evidence of association of the anaesthetic technique with survival outcomes through
randomised controlled trials may take several decades to establish. Such studies are expensive, take a long
period of time, and require extensive follow-up. Hence, they are usually outside the scope of regular

280	anaesthesia research. Decision-making is complex in the absence of such high-quality evidence, because
281	evidence of harm is difficult to establish, though harm may occur in some instances. Therefore,
282	observational data must be carefully assessed, especially when prospective data is inadequate. Adjusted
283	data from observational studies by pooled analysis will be used to overcome confounding factors.
284	Observational studies will not be combined with RCTs or quasi-randomised trials, limiting the influence
285	of study design on the effects measured by this meta-analysis.
286	A recent consensus of experts in the field of anaesthesiology defined the main outcomes to be chosen
287	when evaluating the impact of anaesthesia techniques on cancer outcomes.[25] The endpoints chosen for
288	this systematic review are based on this report. A uniform definition of outcomes of interest is essential to
289	carry out future observational studies and clinical trial protocols.
290	ETHICS AND DISSEMINATION
291	This study is a systematic review with meta-analysis that evaluates data from previously reported studies;
292	hence ethical approval is not required. We plan to publish this study in a peer-reviewed journal.
293	Author Contributions: BLCA is the guarantor of the review and drafted the manuscript. All authors
294	contributed to the inclusion criteria, the risk of bias assessment, and data extraction strategies. FMC and
295	LESF contributed with their knowledge on systematic reviews. LCST and FMC will contribute with
296	epidemiological and statistical analysis. ACM contributed through expertise in medical, and JLO, through
297	expertise in surgical oncology. BLCA contributed with anaesthetic knowledge. BLCA and JLO will
298	screen potential studies, perform duplicate independent data extraction, risk of bias assessment, GRADE
299	assessment. LCST will act as a third reviewer and arbitrator if necessary. All authors read, provided
300	comments, and approved the final version of the protocol.
301	Acknowledgements: We are grateful to acknowledge to Raphael Chanca, the Health Science Librarian
302	who reviewed the systematic review search strategy.
303	Funding: The authors have not received a specific grant for this research from any funding agency in the
304	public, commercial, or not-for-profit sectors.
305	Competing interests: None declared.

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2 3	306	Patient consent: Not required.
4	500	ratient consent: Not required.
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6 7	307	Patient and public involvement: Patients and public were not involved in the development of this
7 8	308	systematic review protocol.
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11 12	309	Provenance and peer review: Not commissioned; externally peer reviewed.
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14	310	Data sharing statement: No additional data from this study are available.
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Appendix 1

Complete search Strategy

Database	Search
Pubmed	1 Anesthesia[MeSH Terms]
	2 Anesthetics[MeSH Terms]
	3 Anesthesiology[MeSH Terms]
	4 Anest*[Title/Abstract]
	5 Anaest*[Title/Abstract]
	6 Analg*[Title/Abstract]
	7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
	8 Melanoma[MeSH Terms]
	9 Melanoma*[Title/Abstract]
	10 #8 OR #9
	11 #7 AND #10
Embase	1 'melanoma'/exp
	2 'fortner melanoma':ti,ab
	3 'malignant melanoma':ti,ab
	4 'malignant melanomatosis':ti,ab
	5 'melanocarcinoma':ti,ab
	6 'melanoma':ti,ab
	7 'melanoma (e)':ti,ab
	8 'melanomalignoma':ti,ab
	9 'naevi and melanomas':ti,ab
	10 'naevocarcinoma':ti,ab
	11 'nevi and melanomas':ti,ab
	12 'nevocarcinoma':ti,ab
	13 'nodular melanoma':ti,ab
	14 'pigmentary cancer':ti,ab
	15 #1 OR# 2 OR #3 OR #4# OR # 5# OR #6# OR# 7
	OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
	OR #14

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'anesthesiological procedure'/exp

'anaesthesia and analgesia':ti,ab

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	45 46 47 48 49 50 51	36 37 38 39 40 41	

	18	'anesthesia and analgesia':ti,ab
	19	'anesthesiological procedure':ti,ab
	20	'anesthesiological techniques':ti,ab
	21	'anesthetic agent'/exp
	22	'anaesthetic':ti,ab
	23	'anaesthetic agent':ti,ab
	24	'anaesthetic drug':ti,ab
	25	'anaesthetics':ti,ab
	26	'anaesthetics, combined':ti,ab
	27	'anaesthetics, dissociative':ti,ab
	28	'anaesthetics, general':ti,ab
	29	'anesthetic':ti,ab
	30	'anesthetic agent':ti,ab
	31	'anesthetic drug':ti,ab
	32	'anesthetics':ti,ab
	33	'anesthetics, combined':ti,ab
	34	'anesthetics, dissociative':ti,ab
	35	'anesthetics, general':ti,ab
	36	'general anaesthetic':ti,ab
	37	'general anaesthetic agent':ti,ab
	38	'general anesthetic':ti,ab
	39	'general anesthetic agent':ti,ab
	40	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR
		#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR
		#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR
		#34 OR #35 OR #36 OR #37 OR #38 OR #39)
	41	#15 AND #40
CENTRAL	1	MeSH descriptor: [Anesthesia] explode all trees
	2	MeSH descriptor: [Anesthetics] explode all trees
	3	MeSH descriptor: [Anesthesiology] explode all

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	4 Anest*:ab,ti,kw	
	5 Anaest*:ab,ti,kw	
	6 #1 OR #2 OR #3 OR #4 OR #5	
	7 MeSH descriptor: [Melanoma] explode all trees	
	8 Melanoma*:ab,ti,kw	
	9 #7 OR #8	
	10 #6 AND #9	
Web of	1 TS=(Anest* OR Anaest*)	
science	2 TS=(Melanoma*)	
	3 #1 AND #2	
Virtual	1 mh:("anesthesia")	
Health	2 mh:("anesthesia and analgesia")	
Library Portal	3 mh:("analgesia and anesthesia")	
(LILACS and	4 mh:("analgesia")	
IBECS)	5 tw:(anest*)	
	6 tw:(analg*)	
	7 #1 OR #2 OR #3 OR #4 OR #5 OR #6	
	8 mh:(Melanoma)	
	9 tw:(Melanoma*)	
	10 #8 OR #9	
	11 #7 AND #10	
International	In the Advanced Search	
Clinical	Title: Anest* OR Anaest* OR Analg*	
Trials	Condition: Melanoma	
Registry	Recruitment status: All	
Platform		
Portal		
OpenGrey	1 Anest*	
	2 Anaest*	
	3 Analg*	
	4 #1 OR #2 OR #3	
	5 Melanoma*	
	6 #4 AND #5	

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 PRISMA-P 2015 Checklist
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 This checklist has been adapted for use with protocol submissions to Systematic Reviews from Table 3 in Moher D et al: Preferred reporting

 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Review 2015 4:1

		reigr				
Section/topic	#	Checklist item	Informatio Yes	on reported No	Line number(s)	
ADMINISTRATIVE IN	FORMAT					
Title		xt a				
Identification	1a	Identify the report as a protocol of a systematic review			3-5	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such $\frac{d}{d} \frac{1}{d} \frac{1}{d} \frac{1}{d}$			125-127	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number Abstract			61; 128-129	
Authors	•	Ģ. Br		•	-	
Contact	3а	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author			7-32	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review			293-300	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, gdentify a such and list changes; otherwise, state plan for documenting important protocol amendments	as 🖂		127-130	
Support		sin on		-	-	
Sources	5a	Indicate sources of financial or other support for the review			115	
Sponsor	5b	Provide name for the review funder and/or sponsor			115	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			115	
NTRODUCTION		ies, at				
Rationale	6	Describe the rationale for the review in the context of what is already known			81-110	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)			115-122	
METHODS						
METHODS		raphique o	(lioN	



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		BMJ Open BMJ Open			Page
Section/topic	#	Checklist item	Informatio Yes	n reported No	Line number(s)
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and repord g characteristics (e.g., years considered, language, publication status) to be used as criteria for y			132-164
nformation sources	9	Describe all intended information sources (e.g., electronic databases, contact with study and s, trial registers, or other grey literature sources) with planned dates of coverage			165-178
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including			179-190
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the to be a second s			191-195
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and be used for selecting studies (e.g., two independent reviewers) and the selecting studies (e.g., two independent reviewers) and the selecting studies (e.g., two independent reviewers) are selected as the selecting studies (e.g., two independent reviewers) are selected as the selecting studies (e.g., two independent reviewers) are selected as the selecting studies (e.g., two independent reviewers) are selected as the se			196-204
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators			196-204
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications			228-262
Dutcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and gadditional outcomes, with rationale			147-155
Risk of bias in ndividual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis			205-220
DATA		sin o	•	•	•
	15a	Describe criteria under which study data will be quantitatively synthesized			214-221
Synthesis	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, nethods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., 1 ² , Kendall's tau)	f		214-221; 228-256
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression	ı) 🛛		256-262
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned			218-227
/leta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)			211-213
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)			263-266

